

April 06, 2007

Roger Citron, R.Ph.
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Helena, MT 59620-2951

Dear Dr. Citron:

Your Senior Regional Scientific Manager, Kate Ryan, has forwarded your request for information regarding CRESTOR® (rosuvastatin calcium).

As per your request, a 2-page overview of recent data on the safety and efficacy of rosuvastatin is included for your review, along with the supporting references.

The above information is supplied to you as a professional courtesy in response to your request. It is intended to provide pertinent data to assist you in forming your own conclusions and making decisions. Prescription drugs used outside of their approved indication may not be eligible for reimbursement by any third-party payors, including Medicaid, Medicare, or similar federal or state programs. AstraZeneca does not recommend the use of CRESTOR in any other manner than as described in the enclosed prescribing information. We hope that you find this information useful. Please complete and return the enclosed survey to help us determine how well we are meeting your expectations. The survey can also be completed online at <http://mrsurvey.astrazeneca-us.com>.

Thank you for your interest in CRESTOR® (rosuvastatin calcium). If we may be of further assistance to you, please contact AstraZeneca at 1-800-236-9933.

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AstraZeneca 

Sincerely,

Nancy Pettineo, Pharm.D.

Senior Medical Information Manager

Enclosure(s):

- CRESTOR Prescribing Information
- Faergeman O, et al on behalf of the ECLIPSE study investigators. Poster presented at: The XIV International Symposium on Atherosclerosis; June 18-22, 2006; Rome, Italy.
- Clearfield MB, et al. *Trials*. 2006;7:35: doi:10.1186/1745-6215-7-35.
- Leiter LA, et al. *Atherosclerosis*. In Press. 2007:doi:10.1016/j.atherosclerosis.2006.12.001.
- Ballantyne C, et al. *Am Heart J*. 2006;151:975e1-975e9.
- Betteridge DJ, et al on behalf of the ANDROMEDA study investigators. *Diabet Med*. In Press. 2007; doi:10.1111/j.1464-5491.2007.02095.x
- Wolffenbuttel BHR, et al on behalf of the Dutch CORALL study group. *J Intern Med*. 2005;257:531-539.
- Lloret R, et al for the STARSHIP Study Group. *Am J Cardiol*. 2006;98:768-773.
- Deedwania P, et al. Abstract presented at the XIV International Symposium on Atherosclerosis; June 18-22, 2006; Rome, Italy.
- Johansson S, et al. *Pharmacoepidemiol Drug Saf*. 2006;15:454-461.
- Bullano MF, et al. *Pharmacotherapy*. 2006;26:469-478.
- Bullano MF, et al. *Am J Health-Syst Pharm*. 2007;64: 276-284.
- McAfee AT, et al. *Pharmacoepidemiol Drug Saf*. 2006;15:444-453.
- Shepherd J, et al. *Cardiology*. 2007;107:433-443.

INQ 602373

Summary for CRESTOR® (Rosuvastatin Calcium) for Montana Medicaid (April 2007)

Overview of Rosuvastatin: Rosuvastatin is a relatively hydrophilic statin capable of providing significant improvements in the lipid profile in a wide variety of adult patient populations with hypercholesterolemia, with and without hypertriglyceridemia, regardless of race, gender, or age.¹ In a dose-ranging study, rosuvastatin produced dose related reductions in LDL-C of 45-63% across the dose range of 5-40mg once daily, decreased TG between 10-35%, and increased HDL-C between 8% and 14%. Rosuvastatin is generally well tolerated and adverse reactions have usually been mild and transient. The post-marketing safety profile of rosuvastatin is consistent with that seen in the clinical trial program and similar to that of other currently marketed statins.² *Please see accompanying full prescribing information for CRESTOR.*

Efficacy in Lowering LDL-C, Modifying Lipid Parameters, and Goal Attainment:

CHD/CHD Risk Equivalents: In the ECLIPSE trial, high-risk patients with hypercholesterolemia were randomized to receive rosuvastatin 10mg or atorvastatin 10mg for 6 weeks and then were force-titrated every 6 weeks until the maximum doses were achieved (rosuvastatin 10/20/40/40mg and atorvastatin 10/20/40/80mg).³ At week 6, LDL-C was reduced to a significantly greater extent with rosuvastatin 10mg compared to atorvastatin 10mg (-47% vs. -39%; p<0.001). Greater LDL-C reductions were seen with rosuvastatin 20mg vs. atorvastatin 20mg at week 12 (-53% vs. -45%; p<0.001), rosuvastatin 40mg vs. atorvastatin 40mg at week 18 (-57% vs. -49%; p<0.001), and rosuvastatin 40mg vs. atorvastatin 80mg at week 24 (-57% vs. -52%; p<0.001). Rosuvastatin increased HDL-C and reduced TG at each 6-week time point. At 24 weeks, significantly more patients reached NCEP ATP III LDL-C goal (<100 mg/dL) with rosuvastatin vs. atorvastatin (83.6% vs. 74.6%; p<0.001). In addition, more very high-risk patients on rosuvastatin compared to atorvastatin achieved updated ATP III LDL-C goals (<70 mg/dL) at 24 weeks (38% vs. 20.2%; p<0.001).⁴

In the PULSAR trial, the efficacy and safety of rosuvastatin 10mg and atorvastatin 20mg was compared in high-risk patients with hypercholesterolemia.⁵ After 6 weeks, LDL-C levels were reduced significantly more with rosuvastatin 10mg than with atorvastatin 20mg (-45% vs. -43%, p<0.05). Rosuvastatin increased HDL-C and reduced TG at 6 weeks. More patients in the rosuvastatin 10mg group than in the atorvastatin 20mg group achieved NCEP ATP III LDL-C goal <100 mg/dL (69% vs. 63%, respectively, p<0.05).

In the POLARIS trial, comparing rosuvastatin 40mg and atorvastatin 80mg in high-risk patients, rosuvastatin produced significantly greater reductions LDL-C levels (-56% vs. -52%; p<0.001) at 8 weeks.⁶ Rosuvastatin increased HDL-C and reduced TG at 8 weeks. Significantly more patients reached NCEP ATP III LDL-C goal (<100 mg/dL) with rosuvastatin vs. atorvastatin at 8 weeks (80% vs. 72%; p<0.01). In addition, more very high-risk patients on rosuvastatin compared to atorvastatin achieved updated ATP III LDL-C goals (<70 mg/dL) at 8 weeks (36% vs. 18%; p<0.001).⁴

In the MERCURY II study, a 16-week, 2-period (8 weeks each) trial, significantly more high-risk patients who were switched from atorvastatin 10mg or simvastatin 20mg to rosuvastatin 10mg after 8 weeks of therapy reached their LDL-C goal (<100mg/dL) than those who remained on their original statin (rosuvastatin 10mg vs. atorvastatin 10mg: 66% vs. 42%; p<0.001; rosuvastatin 10mg vs. simvastatin 20mg: 73% vs. 32%; p<0.001).⁷ The same was true for those switched to rosuvastatin 20mg from atorvastatin 20mg (64% vs. 79%; p<0.001) or simvastatin 40mg (rosuvastatin 20mg vs. simvastatin 40mg: 84% vs. 56%; p<0.001). In addition, switching to rosuvastatin resulted in greater decreases in LDL-C than continuing atorvastatin or simvastatin (all within-arm comparisons p<0.001). Treatment with rosuvastatin also resulted in increased HDL-C levels and decreased TG levels.

Diabetes: In the ANDROMEDA study, dyslipidemic patients with type 2 diabetes were administered rosuvastatin 10mg or atorvastatin 10mg for 8 weeks followed by titration to 20mg for each drug for an additional 8 weeks.⁸ After both 8 and 16 weeks of treatment, rosuvastatin provided significantly greater reductions in LDL-C (8 wks: -51% vs. -39%; 16 wks: -57% vs. -46%; both p<0.001). Treatment with rosuvastatin also resulted in increased HDL-C levels and decreased TG levels.

In the CORALL trial, dyslipidemic patients with type 2 diabetes were randomized to receive rosuvastatin 10mg or atorvastatin 20mg for 6 weeks and then were force-titrated every 6 weeks until the maximum doses were achieved (rosuvastatin 10/20/40mg and atorvastatin 20/40/80mg).⁹ At 18 weeks, rosuvastatin 40mg resulted in significantly greater reductions in LDL-C compared with atorvastatin 80mg (-54% vs. -48%; p<0.01). Reductions were seen in HDL-C and TG levels at 18 weeks. Significantly more patients receiving rosuvastatin reached NCEP ATP III <100 mg/dL goal at week 18 (91.5% vs. 81.1% for rosuvastatin 40mg and atorvastatin 80mg respectively; p<0.05).

Ethnic Populations: The STARSHIP trial evaluated the efficacy of rosuvastatin 10mg and 20mg with atorvastatin 10mg and 20mg in Hispanic patients with hypercholesterolemia and a 10-year CHD risk of ≥10%, CHD, or a CHD risk equivalent over a 6-week period.¹⁰ Rosuvastatin 10mg reduced LDL-C by -45% compared with -36% by atorvastatin 10mg (p<0.0001). LDL-C was reduced by -50% vs. -42% with rosuvastatin 20mg and atorvastatin 20mg respectively (p<0.0001). In addition, rosuvastatin increased HDL-C and reduced TG. The patients reaching NCEP ATP III LDL-C goals were: rosuvastatin 10mg 78%, rosuvastatin 20mg 88%, atorvastatin 10mg 60%, and atorvastatin 20mg 73%.

The IRIS trial evaluated the efficacy of rosuvastatin 10mg and 20mg compared to atorvastatin 10mg and 20mg in South Asian patients in the US and Canada with hypercholesterolemia and a 10-year CHD risk of ≥10%, CHD, or a CHD risk equivalent over a 6-week period.¹¹ Rosuvastatin 10mg reduced LDL-C by -45% compared with -40% by atorvastatin 10mg (p<0.017). LDL-C was reduced by -50% vs. -47% with rosuvastatin 20mg and atorvastatin 20mg respectively (p=NS). In addition, rosuvastatin increased HDL-C and reduced TG. The patients reaching NCEP ATP III LDL-C goals were: rosuvastatin 10mg 78.7%, rosuvastatin 20mg 88.9%, atorvastatin 10mg 76.1%, and atorvastatin 20mg 84.6%.

Real-World Data: AstraZeneca has conducted trials to examine the efficacy of rosuvastatin outside of clinical trials. In addition, AstraZeneca has developed a progressive, comprehensive pharmacoepidemiology program, which includes nine studies assessing over 50,000 patients treated with rosuvastatin.^{12,13} It consists of three components: patient characteristic studies (4 studies), safety evaluation studies (4 studies); and review of data generated from the Prescription-Event Monitoring (PEM) study, designed and run by an independent third party. The studies included in the program are observational and will be conducted in the US, Netherlands, Canada, and the UK.

Real-World Efficacy: The effect of rosuvastatin was compared with other statins on lipid levels and NCEP ATP III LDL-C goal attainment in a usual care setting, using medical and pharmacy administrative claims from a large managed care health plan.¹⁴ Patients treated with rosuvastatin experienced significantly greater percent reductions in LDL-C than patients treated with other statins, such as atorvastatin and simvastatin (-33% vs. -24% and -20%, respectively; p<0.05). In addition, significantly more patients treated with rosuvastatin attained ATP III LDL-C goal than patients treated with other statins, such as atorvastatin and simvastatin (64% vs. 57% and 55%, respectively; p<0.05).

A retrospective, longitudinal, cohort analysis of newly-initiated rosuvastatin or atorvastatin patients from a large western U.S. health plan compared the effects on lipid levels and achievement of NCEP ATP III LDL-C goals in a usual care setting.¹⁵ Compared to atorvastatin, rosuvastatin treatment resulted in greater reductions in total-C, LDL-C, and non-HDL-C ($p<0.001$). Rosuvastatin 10mg provided greater LDL-C reductions than atorvastatin 10mg (-36% vs. -26%, respectively, $p<0.001$). There were no significant differences between groups for change in HDL-C or TG levels. ATP III LDL-C goals were reached by 74% of the rosuvastatin group compared to 65% of the atorvastatin group ($p=0.088$). After adjusting for age, gender, percent change in LDL-C required to reach goal, NCEP risk strata, and duration of therapy, patients on rosuvastatin were significantly more likely to attain the ATP III LDL-C goal as compared to patients receiving atorvastatin (OR=1.87, 95% CI: 1.10-3.17; $p<0.05$).

Pharmacoepidemiology: A retrospective matched cohort study was designed to compare incidence rates of hospitalization with rhabdomyolysis, myopathy, renal, or hepatic dysfunction, and in-hospital deaths, between initiators of rosuvastatin and other statins in the United States.¹⁶ The study found no difference between rosuvastatin and other statins in the incidence of hospitalizations associated with renal or hepatic events or in-hospital deaths. The incidence rates of rhabdomyolysis and myopathy were low among all groups but were too small for firm conclusions to be drawn on any difference between the statins.

Drug Interactions: Rosuvastatin is minimally metabolized (10%) by the P450 2C9 and clearance is not dependent on metabolism by the cytochrome P450 3A4 pathway to a clinically significant extent.¹ No clinically significant drug interactions with erythromycin, fenofibrate, ezetimibe, digoxin or the azole antifungals. Important drug interactions include antacids, cyclosporine, gemfibrozil, lopinavir/ritonavir, and warfarin.

Safety:

General: The safety and tolerability of rosuvastatin was examined using data from a multinational phase II/III/IIIb/IV program of 16,876 patients (25,670 patient-years) who received rosuvastatin 5-40mg.¹⁷ Patients were demographically diverse, with a variety of dyslipidemias and comorbidities (CHD [40.3%], diabetes [21.9%], hypertension [49.1%], and mild to severe renal impairment [95.0%]). Many patients received rosuvastatin for over a year (≥ 48 weeks: 10,103 [59.9%]; ≥ 96 weeks: 6,449 [38.2%]). In placebo-controlled trials, the rate of AEs irrespective of causality assessment was similar for rosuvastatin and placebo groups (52.1% and 51.8%, respectively). Rates of AEs were also similar for controlled clinical trials with comparator statins (rosuvastatin 5-40mg, atorvastatin 10-80mg, simvastatin 10-80mg, and pravastatin 10-40mg).

In controlled trials, clinically significant ALT elevations (>3 times ULN on ≥ 2 consecutive measurements) occurred in 0.2% of the rosuvastatin 5-40mg, atorvastatin 10-80mg, and pravastatin 10-40mg groups, and 0.1% of the simvastatin 10-80mg group. Overall, the occurrence of CK elevations $>10\times$ ULN was low across statin groups: rosuvastatin 5-40mg (0.3%), atorvastatin 10-80mg (0.1%), simvastatin 10-80mg (0.2%), and pravastatin 10-40mg (0%). Myalgia, irrespective of causality, was reported in 3.5% of patients receiving rosuvastatin 5-40mg. Dipstick positive proteinuria occurred in $<1.0\%$ of the rosuvastatin 5-20mg, atorvastatin 10-80mg, simvastatin 20-80mg, pravastatin 20-40mg, and placebo groups and in 1.5% of the rosuvastatin 40mg group. Serum creatinine decreased across the dose groups and small changes in estimated glomerular filtration rate (eGFR) were observed. The magnitude of change in eGFR tended to increase over the duration of treatment and did not appear to be dose-related.

Post-Marketing Safety Update: The following information, which was updated in February 2007, summarizes the cumulative post-marketing data on serious adverse event reports for rosuvastatin.² The spontaneous reporting frequency of myopathy and rhabdomyolysis, in patients taking rosuvastatin, is very rare ($<1/10,000$), which is consistent with that reported with other currently marketed statins. As with other marketed statins, there is a higher reporting rate of rhabdomyolysis for the highest marketed dose of rosuvastatin. As with other currently marketed statins, AstraZeneca has received very rare reports ($<1/10,000$) of hepatitis and jaundice as well as rare reports ($<1/1,000$) of increased hepatic transaminases in patients taking rosuvastatin. AstraZeneca has also received very rare reports of hepatic events with a fatal outcome. A medical review of these fatal reports does not establish a causal relationship to rosuvastatin because reports with sufficient information for assessment either had more likely alternative causes or had confounding factors for the fatal outcome. The spontaneous reporting frequency of renal failure, in patients taking rosuvastatin is very rare ($<1/10,000$), which is consistent with that reported with other marketed statins. Based on a medical review of the spontaneous reports, there is insufficient information to establish a causal relationship between rosuvastatin and renal failure. AstraZeneca continues to monitor post-marketing adverse event reports rigorously and dedicates intensive efforts to follow up reports and evaluate cases. The post-marketing safety profile of rosuvastatin is consistent with that seen in the clinical trial program and similar to that of other currently marketed statins.

AstraZeneca is Committed to Ongoing Research with CRESTOR: The GALAXY Program is a large, comprehensive, long-term and evolving global research initiative investigating cardiovascular risk reduction with rosuvastatin. The studies in the GALAXY Program include atherogenic lipid profile studies, atherosclerosis studies (ASTEROID, METEOR, and ORION trials) and reduction of cardiovascular morbidity and mortality studies (AURORA, CORONA, and JUPITER trials).

Reference(s):

¹ CRESTOR Prescribing Information.

² Rosuvastatin Information Website. Available at: <http://www.rosuvastatininformation.com>. Accessed on March 21, 2007.

³ Faergeman O, et al on behalf of the ECLIPSE study investigators. Poster presented at: The XIV International Symposium on Atherosclerosis; June 18-22, 2006; Rome, Italy.

⁴ Grundy SM, et al. *Circulation*. 2004;110:227-239.

⁵ Clearfield MB, et al. *Trials*. 2006;7:35. doi:10.1186/1745-6215-7-35.

⁶ Leiter LA, et al. *Atherosclerosis*. In Press. 2007;doi:10.1016/j.atherosclerosis.2006.12.001.

⁷ Ballantyne C, et al. *Am Heart J*. 2006;151:975e1-975e9.

⁸ Betteridge DJ, et al on behalf of the ANDROMEDA study investigators. *Diabet Med*. In Press. 2007; doi:10.1111/j.1464-5491.2007.02095.x

⁹ Wolffenbutter BHR, et al on behalf of the Dutch CORALL study group. *J Intern Med*. 2005;257:531-539.

¹⁰ Lloret R, et al for the STARSHIP Study Group. *Am J Cardiol*. 2006;98:768-773.

¹¹ Deedwania P, et al. Abstract presented at the XIV International Symposium on Atherosclerosis; June 18-22, 2006; Rome, Italy.

¹² Rosuvastatin Information Website. Available at: www.rosuvastatininformation.com. Accessed on March 21, 2007.

¹³ Johansson S, et al. *Pharmacoepidemiol Drug Saf*. 2006;15:454-461.

¹⁴ Bullano MF, et al. *Pharmacotherapy*. 2006;26:469-478.

¹⁵ Bullano MF, et al. *Am J Health-Syst Pharm*. 2007;64: 276-284.

¹⁶ McAfee AT, et al. *Pharmacoepidemiol Drug Saf*. 2006;15:444-453.

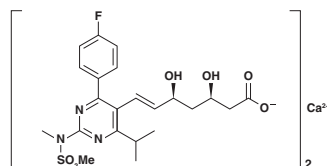
¹⁷ Shepherd J, et al. *Cardiology*. 2007;107:433-443.



DESCRIPTION

CRESTOR® (rosuvastatin calcium) is a synthetic lipid-lowering agent. Rosuvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[(methyl(methylsulfonyl)amino) pyrimidin-5-yl]] (3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$. Its molecular weight is 1001.14. Its structural formula is:



Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0.

CRESTOR Tablets for oral administration contain 5, 10, 20, or 40 mg of rosuvastatin and the following inactive ingredients: microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, croscopolone NF, magnesium stearate NF, hypromellose NF, triacetin NF, titanium dioxide USP, yellow ferric oxide, and red ferric oxide NF.

CLINICAL PHARMACOLOGY

General: In the bloodstream, cholesterol and triglycerides (TG) circulate as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) fractions that contain apolipoprotein B-100 (ApoB-100) and high-density lipoprotein (HDL) fractions.

Cholesterol and TG synthesized in the liver are incorporated into VLDL and secreted into the circulation for delivery to peripheral tissues. TG are removed by the action of lipases, and in a series of steps, the modified VLDL is transformed first into IDL and then into cholesterol-rich LDL. IDL and LDL are removed from the circulation mainly by high affinity ApoB/E receptors, which are expressed to the greatest extent on liver cells. HDL is hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver.

Epidemiologic, experimental, and clinical studies have established that high LDL cholesterol (LDL-C), low HDL cholesterol (HDL-C), and high plasma TG promote human atherosclerosis and are risk factors for developing cardiovascular disease. In contrast, higher levels of HDL-C are associated with decreased cardiovascular risk.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Mechanism of Action: Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of cholesterol. *In vivo* studies in animals, and *in vitro* studies in cultured animal and human cells have shown rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabo-

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lism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

Rosuvastatin reduces total cholesterol (total-C), LDL-C, ApoB, and nonHDL-C (total cholesterol minus HDL-C) in patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Rosuvastatin also reduces TG and produces increases in HDL-C. Rosuvastatin reduces total-C, LDL-C, VLDL-cholesterol (VLDL-C), ApoB, nonHDL-C and TG, and increases HDL-C in patients with isolated hypertriglyceridemia. The effect of rosuvastatin on cardiovascular morbidity and mortality has not been determined.

Pharmacokinetics and Drug Metabolism

Absorption: In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both peak concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%.

Administration of rosuvastatin with food decreased the rate of drug absorption by 20% as assessed by C_{max} , but there was no effect on the extent of absorption as assessed by AUC.

Plasma concentrations of rosuvastatin do not differ following evening or morning drug administration.

Significant LDL-C reductions are seen when rosuvastatin is given with or without food, and regardless of the time of day of drug administration.

Distribution: Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Metabolism: Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin.

Excretion: Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours.

After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

Special Populations

Race: A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group. (See WARNINGS, Myopathy/Rhabdomyolysis, PRECAUTIONS, General and DOSAGE AND ADMINISTRATION.)

Gender: There were no differences in plasma concentrations of rosuvastatin between men and women.

Geriatric: There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥ 65 years).

Pediatric: In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10 to 17 years of age with heterozygous FH received single and multiple oral doses of rosuvastatin. Both C_{max} and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses.

Renal Insufficiency: Mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min/ $1.73m^2$) had no influence on plasma concentrations of rosuvastatin when oral doses of 20 mg rosuvastatin were administered for 14 days. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment ($CL_{cr} < 30$ mL/min/ $1.73m^2$) compared with healthy subjects ($CL_{cr} > 80$ mL/min/ $1.73m^2$) (see PRECAUTIONS, General).

Hemodialysis: Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Hepatic Insufficiency: In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly

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increased. In patients with Child-Pugh A disease, C_{max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function (see CONTRAINDICATIONS and WARNINGS, Liver Enzymes).

Drug-Drug Interactions

Cytochrome P450 3A4: *In vitro* and *in vivo* data indicate that rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. This has been confirmed in studies with known cytochrome P450 3A4 inhibitors (ketoconazole, erythromycin, itraconazole).

Ketoconazole: Coadministration of ketoconazole (200 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in no change in plasma concentrations of rosuvastatin.

Erythromycin: Coadministration of erythromycin (500 mg four times daily for 7 days) with rosuvastatin (80 mg) decreased AUC and C_{max} of rosuvastatin by 20% and 31%, respectively. These reductions are not considered clinically significant.

Itraconazole: Itraconazole (200 mg once daily for 5 days) resulted in a 39% and 28% increase in AUC of rosuvastatin after 10 mg and 80 mg dosing, respectively. These increases are not considered clinically significant.

Fluconazole: Coadministration of fluconazole (200 mg once daily for 11 days) with rosuvastatin (80 mg) resulted in a 14% increase in AUC of rosuvastatin. This increase is not considered clinically significant.

Cyclosporine: Coadministration of cyclosporine with rosuvastatin resulted in no significant changes in cyclosporine plasma concentrations. However, C_{max} and AUC of rosuvastatin increased 11- and 7-fold, respectively, compared with historical data in healthy subjects. These increases are considered to be clinically significant (see PRECAUTIONS, Drug Interactions, WARNINGS, Myopathy/Rhabdomyolysis, and DOSAGE AND ADMINISTRATION).

Warfarin: Coadministration of warfarin (25 mg) with rosuvastatin (40 mg) did not change warfarin plasma concentrations but increased the International Normalized Ratio (INR) (see PRECAUTIONS, Drug Interactions).

Digoxin: Coadministration of digoxin (0.5 mg) with rosuvastatin (40 mg) resulted in no change to digoxin plasma concentrations.

Fenofibrate: Coadministration of fenofibrate (67 mg three times daily) with rosuvastatin (10 mg) resulted in no significant changes in plasma concentrations of rosuvastatin or fenofibrate (see PRECAUTIONS, Drug Interactions, and WARNINGS, Myopathy/Rhabdomyolysis).

Gemfibrozil: Coadministration of gemfibrozil (600 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in a 90% and 120% increase for AUC and C_{max} of rosuvastatin, respectively. This increase is considered to be clinically significant (see PRECAUTIONS, Drug Interactions, WARNINGS, Myopathy/Rhabdomyolysis, DOSAGE AND ADMINISTRATION).

Ezetimibe: Coadministration of ezetimibe (10 mg) with rosuvastatin (40 mg) resulted in no significant changes in plasma concentrations of rosuvastatin or ezetimibe.

Antacid: Coadministration of an antacid (aluminum and magnesium hydroxide combination) with rosuvastatin (40 mg) resulted in a decrease in plasma concentrations of rosuvastatin by 54%. However, when the antacid was given 2 hours after rosuvastatin, there were no clinically significant changes in plasma concentrations of rosuvastatin (see PRECAUTIONS, Information for Patients).

Oral contraceptives: Coadministration of oral contraceptives (ethinyl estradiol and norgestrel) with rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively.

Lopinavir/Ritonavir: Coadministration of CRESTOR and a combination product of two protease inhibitors (400 mg lopinavir/100 mg ritonavir) in healthy volunteers was associated with an approximately 2-fold and 5-fold increase in rosuvastatin steady-state AUC₍₀₋₂₄₎ and C_{max} respectively. Interactions between CRESTOR and other protease inhibitors have not been examined. (See PRECAUTIONS, Drug Interactions.)

Clinical Studies

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb)

CRESTOR reduces total-C, LDL-C, ApoB, nonHDL-C, and TG, and increases HDL-C, in patients with hypercholesterolemia and

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mixed dyslipidemia. Therapeutic response is seen within 1 week, and maximum response is usually achieved within 4 weeks and maintained during long-term therapy.

CRESTOR is effective in a wide variety of adult patient populations with hypercholesterolemia, with and without hypertriglyceridemia, regardless of race, gender, or age and in special populations such as diabetics or patients with heterozygous FH. Experience in pediatric patients has been limited to patients with homozygous FH.

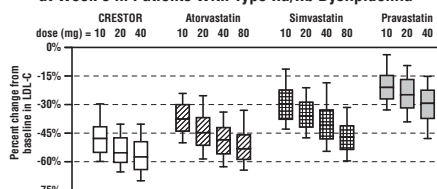
Dose-Ranging Study: In a multicenter, double-blind, placebo-controlled, dose-ranging study in patients with hypercholesterolemia, CRESTOR given as a single daily dose for 6 weeks significantly reduced total-C, LDL-C, nonHDL-C, and ApoB, across the dose range (Table 1).

Table 1. Dose-Response in Patients With Primary Hypercholesterolemia (Adjusted Mean % Change From Baseline at Week 6)

Dose	N	Total-C	LDL-C	nonHDL-C	ApoB	TG	HDL-C
Placebo	13	-5	-7	-7	-3	-3	3
5	17	-33	-45	-44	-38	-35	13
10	17	-36	-52	-48	-42	-10	14
20	17	-40	-55	-51	-46	-23	8
40	18	-46	-63	-60	-54	-28	10

Active-Controlled Study: CRESTOR was compared with the HMG-CoA reductase inhibitors atorvastatin, simvastatin, and pravastatin in a multicenter, open-label, dose-ranging study of 2,240 patients with Type IIa and IIb hypercholesterolemia. After randomization, patients were treated for 6 weeks with a single daily dose of either CRESTOR, atorvastatin, simvastatin, or pravastatin (Figure 1 and Table 2).

Figure 1. Percent LDL-C Change by Dose of CRESTOR, Atorvastatin, Simvastatin, and Pravastatin at Week 6 in Patients With Type IIa/IIb Dyslipidemia



Box plots are a representation of the 25th, 50th, and 75th percentile values, with whiskers representing the 10th and 90th percentile values. Mean baseline LDL-C: 189 mg/dL.

Table 2. Percent Change in LDL-C From Baseline to Week 6 (LS means §) by Treatment Group (sample sizes ranging from 156-167 patients per group)

Treatment	10 mg	20 mg	40 mg	80 mg
CRESTOR	-46*	-52†	-55‡	—
Atorvastatin	-37	-43	-48	-51
Pravastatin	-20	-24	-30	—
Simvastatin	-28	-35	-39	-46

* CRESTOR 10 mg reduced LDL-C significantly more than atorvastatin 10 mg; pravastatin 10 mg, 20 mg, and 40 mg; simvastatin 10 mg, 20 mg, and 40 mg. (p<0.002)

† CRESTOR 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. (p<0.002)

‡ CRESTOR 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg and 80 mg (p<0.002)

§ Corresponding standard errors are approximately 1.00

Heterozygous Familial Hypercholesterolemia

In a study of patients with heterozygous FH (baseline mean LDL of 291), patients were randomized to CRESTOR 20 mg or atorvastatin 20 mg. The dose was increased by 6-week intervals. Significant LDL-C reductions from baseline were seen at each dose in both treatment groups (Table 3).

Table 3. Mean LDL-C Percentage Change From Baseline

		CRESTOR (n=435)	Atorvastatin (n=187)
		LS Mean* (95% CI)	LS Mean (95% CI)
Week 6	20 mg	-47% (-49%, -46%)	-38% (-40%, -36%)
Week 12	40 mg	-55% (-57%, -54%)	-47% (-49%, -45%)
Week 18	80 mg	NA	-52% (-54%, -50%)

* LS Means are least square means adjusted for baseline LDL.

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Hypertriglyceridemia (Fredrickson Type IIb & IV)

In a double-blind, placebo-controlled dose-response study in patients with baseline TG levels from 273 to 817 mg/dL, CRESTOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels (Table 4).

Table 4. Dose-Response in Patients With Primary Hypertriglyceridemia Over 6 Weeks Dosing Median (Min, Max) Percent Change From Baseline

Dose	Placebo N=26	CRESTOR 5 mg N=25	CRESTOR 10 mg N=23	CRESTOR 20 mg N=27	CRESTOR 40 mg N=25
Triglycerides	1 (-40, 72)	-21 (-58, 38)	-37 (-65, 5)	-37 (-72, 11)	-43 (-80, -7)
nonHDL-C	2 (-13, 19)	-29 (-43, -8)	-49 (-59, -20)	-43 (-74, -12)	-51 (-62, -6)
VLDL-C	2 (-36, 53)	-25 (-62, 49)	-48 (-72, 14)	-49 (-83, 20)	-56 (-83, 10)
Total-C	1 (-13, 17)	-24 (-40, -4)	-40 (-51, -14)	-34 (-61, -11)	-40 (-51, -4)
LDL-C	5 (-30, 52)	-28 (-71, 2)	-45 (-59, 7)	-31 (-66, 34)	-43 (-61, -3)
HDL-C	-3 (-25, 18)	3 (-38, 33)	8 (-8, 24)	22 (-5, 50)	17 (-14, 63)

Homozygous Familial Hypercholesterolemia

In an open-label, forced-titration study, homozygous FH patients (n=40, 8-63 years) were evaluated for their response to CRESTOR 20 to 40 mg titrated at a 6-week interval. In the overall population, the mean LDL-C reduction from baseline was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL lowering of greater than 6%. In the 27 patients with at least a 15% reduction in LDL-C, the mean LDL-C reduction was 30% (median 28% reduction). Among 13 patients with an LDL-C reduction of <15%, 3 had no change or an increase in LDL-C. Reductions in LDL-C of 15% or greater were observed in 3 of 5 patients with known receptor negative status.

INDICATIONS AND USAGE

CRESTOR is indicated:

- as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb);
- as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
- to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

According to NCEP-ATP III guidelines, therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for coronary heart disease due to hypercholesterolemia. The two major modalities of LDL-lowering therapy are therapeutic lifestyle changes (TLC) and drug therapy. The TLC Diet stresses reductions in saturated fat and cholesterol intake. Table 5 defines LDL-C goals and cutpoints for initiation of TLC and for drug consideration.

Table 5. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal	LDL level at which to initiate TLC	LDL level at which to consider drug therapy
CHD ^a or CHD Risk Equivalent (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional) ^b
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	≥130 mg/dL 10-year risk 10-20% ≥160 mg/dL 10-year risk <10%
0-1 Risk Factor ^c	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL) (LDL-lowering drug optional)

^a CHD = coronary heart disease.

^b Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C <100 mg/dL cannot be achieved by TLC. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrates. Clinical judgment also may call for deferring drug therapy in this subcategory.

^c Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, nonHDL-C (total-C minus HDL-C) becomes a secondary target of therapy. NonHDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

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At the time of hospitalization for a coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dL (see NCEP Treatment Guidelines, above).

Patients >20 years of age should be screened for elevated cholesterol levels every 5 years.

Prior to initiating therapy with CRESTOR, secondary causes for hypercholesterolemia (e.g., poorly-controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dyslipoproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG < 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.2 x [TG] + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

CRESTOR has not been studied in Fredrickson Type I, III, and V dyslipidemias.

CONTRAINDICATIONS

CRESTOR is contraindicated in patients with a known hypersensitivity to any component of this product.

Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases (see WARNINGS, Liver Enzymes).

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ROSUVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.

It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with rosuvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended.

Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin (see CONTRAINDICATIONS).

Myopathy/Rhabdomyolysis

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in rosuvastatin-treated patients (see ADVERSE REACTIONS). Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2% to

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0.4% of patients taking rosuvastatin at doses of up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In postmarketing experience, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥65 years), hypothyroidism, and renal insufficiency.

Consequently:

1. Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as, renal impairment (see DOSAGE AND ADMINISTRATION), advanced age, and inadequately treated hypothyroidism.
2. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.
3. The 40 mg dose of rosuvastatin is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of rosuvastatin once daily (see DOSAGE AND ADMINISTRATION).
4. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies or cyclosporine, (see CLINICAL PHARMACOLOGY, Drug Interactions, PRECAUTIONS, Drug Interactions, and DOSAGE AND ADMINISTRATION). **The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with rosuvastatin and gemfibrozil should generally be avoided. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Drug Interactions).**
5. **The risk of myopathy during treatment with rosuvastatin may be increased in circumstances which increase rosuvastatin drug levels (see CLINICAL PHARMACOLOGY, Special Populations, Race and Renal Insufficiency, and PRECAUTIONS, General).**
6. **Rosuvastatin therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).**

PRECAUTIONS

General

Before instituting therapy with rosuvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet and exercise, weight reduction in obese patients, and treatment of underlying medical problems (see INDICATIONS AND USAGE).

Administration of rosuvastatin 20 mg to patients with severe renal impairment ($CL_{cr} < 30$ mL/min/1.73 m²) resulted in a 3-fold increase in plasma concentrations of rosuvastatin compared with healthy volunteers (see WARNINGS, Myopathy/Rhabdomyolysis and DOSAGE AND ADMINISTRATION).

The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients. (See WARNINGS, Myopathy/Rhabdomyolysis; CLINICAL PHARMACOLOGY, Special Populations, Race, and DOSAGE AND ADMINISTRATION.)

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

When taking rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration (see CLINICAL PHARMACOLOGY, Drug Interactions).

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Laboratory Tests

In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on rosuvastatin 40 mg therapy with unexplained persistent proteinuria during routine urinalysis testing.

Drug Interactions

Cyclosporine: When rosuvastatin 10 mg was coadministered with cyclosporine in cardiac transplant patients, rosuvastatin mean C_{max} and mean AUC were increased 11-fold and 7-fold, respectively, compared with healthy volunteers. These increases are considered to be clinically significant and require special consideration in the dosing of rosuvastatin to patients taking concomitant cyclosporine (see WARNINGS, Myopathy/Rhabdomyolysis, and DOSAGE AND ADMINISTRATION).

Warfarin: Coadministration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). In patients taking coumarin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR time has been documented, INR can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of rosuvastatin is changed, the same procedure should be repeated. Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants.

Gemfibrozil: Coadministration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in a 2.2- and 1.9-fold, respectively, increase in mean C_{max} and mean AUC of rosuvastatin (see DOSAGE AND ADMINISTRATION).

Lopinavir/Ritonavir: Coadministration of CRESTOR and a combination product of two protease inhibitors (400 mg lopinavir/100 mg ritonavir) in healthy volunteers was associated with an approximately 2-fold and 5-fold increase in rosuvastatin steady-state AUC₍₀₋₂₄₎ and C_{max} respectively. These increases should be considered when initiating and titrating CRESTOR in patients with HIV taking lopinavir/ritonavir.

Endocrine Function

Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if any HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

CNS Toxicity

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at day 24 at 90 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/day based on AUC comparisons). Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC comparisons). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC comparisons). Retinal dysplasia and retinal loss were seen in dogs treated for 4 weeks by oral gavage at 90 mg/kg/day (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Doses ≤30 mg/kg/day (systemic exposures ≤60 times the human exposure at 40 mg/day based on AUC comparisons) following treatment up to one year, did not reveal retinal findings.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine

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stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses.

In a 107-week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test.

In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times human exposure at 40 mg/day based on AUC comparisons). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times human exposure at 40 mg/day based on body surface area comparisons. Similar findings have been seen with other drugs in this class.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Rosuvastatin may cause fetal harm when administered to a pregnant woman. Rosuvastatin is contraindicated in women who are or may become pregnant. Safety in pregnant women has not been established. There are no adequate and well-controlled studies of rosuvastatin in pregnant women. Rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18. If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus.

In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating and continuing through day 7 post-coitus results in decreased fetal body weight (female pups) and delayed ossification at the high dose (systemic exposures 10 times human exposure at 40 mg/day based on AUC comparisons).

In pregnant rats given oral gavage doses of 2, 10, 50 mg/kg/day from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, systemic exposures ≥12 times human exposure at 40 mg/day based on body surface area comparisons.

In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation day 6 to lactation day 18 (weaning), exposures equivalent to human exposure at 40 mg/day based on body surface area comparisons, decreased fetal viability and maternal mortality was observed.

Rosuvastatin was not teratogenic in rats at ≤25 mg/kg/day or in rabbits ≤3 mg/kg/day (systemic exposures equivalent to human exposure at 40 mg/day based on AUC or body surface comparison, respectively).

Nursing Mothers

It is not known whether rosuvastatin is excreted in human milk. Studies in lactating rats have demonstrated that rosuvastatin is secreted into breast milk at levels 3 times higher than that obtained in the plasma following oral gavage dosing. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rosuvastatin, a decision should be made whether to discontinue nursing or administration of rosuvastatin taking into account the importance of the drug to the lactating woman.

Pediatric Use

The safety and effectiveness in pediatric patients have not been established. Treatment experience with rosuvastatin in a pediatric population is limited to 8 patients with homozygous FH. None of these patients was below 8 years of age.

Geriatric Use

Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years of age. (See WARNINGS, Myopathy/Rhabdomyolysis.)

The efficacy of rosuvastatin in the geriatric population (≥65 years of age) was comparable to the efficacy observed in the non-elderly.

ADVERSE REACTIONS

Rosuvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. In clinical studies of 10,275 patients, 3.7% were discontinued due to adverse experiences attributable to rosuvastatin. The most frequent adverse events thought to be related to rosuvastatin were myalgia, constipation, asthenia, abdominal pain, and nausea.

Clinical Adverse Experiences

Adverse experiences, regardless of causality assessment, reported in ≥2% of patients in placebo-controlled clinical studies of rosuvastatin are shown in Table 6; discontinuations due to adverse events in these studies of up to 12 weeks duration occurred in 3% of patients on rosuvastatin and 5% on placebo.

Table 6. Adverse Events in Placebo-Controlled Studies

Adverse event	Rosuvastatin N=744	Placebo N=382
Pharyngitis	9.0	7.6
Headache	5.5	5.0
Diarrhea	3.4	2.9
Dyspepsia	3.4	3.1
Nausea	3.4	3.1
Myalgia	2.8	1.3
Asthenia	2.7	2.6
Back pain	2.6	2.4
Flu syndrome	2.3	1.8
Urinary tract infection	2.3	1.6
Rhinitis	2.2	2.1
Sinusitis	2.0	1.8

In addition, the following adverse events were reported, regardless of causality assessment, in ≥1% of 10,275 patients treated with rosuvastatin in clinical studies. The events in *italics* occurred in ≥2% of these patients.

Body as a Whole: *Abdominal pain, accidental injury, chest pain, infection, pain, pelvic pain, and neck pain.*

Cardiovascular System: *Hypertension*, angina pectoris, vaso-dilatation, and palpitation.

Digestive System: *Constipation, gastroenteritis*, vomiting, flatulence, periodontal abscess, and gastritis.

Endocrine: Diabetes mellitus.

Hemic and Lymphatic System: Anemia and ecchymosis.

Metabolic and Nutritional Disorders: *Peripheral edema.*

Musculoskeletal System: *Arthritis, arthralgia*, and pathological fracture.

Nervous System: *Dizziness, insomnia, hypertonia, paresthesia, depression, anxiety, vertigo, and neuralgia.*

Respiratory System: *Bronchitis, cough increased*, dyspnea, pneumonia, and asthma.

Skin and Appendages: *Rash* and pruritus.

Laboratory Abnormalities: In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. (See PRECAUTIONS, Laboratory Tests.)

Other abnormal laboratory values reported were elevated creatine phosphokinase, transaminases, hyperglycemia, glutamyl transpeptidase, alkaline phosphatase, bilirubin, and thyroid function abnormalities.

Other adverse events reported less frequently than 1% in the rosuvastatin clinical study program, regardless of causality assessment, included arrhythmia, hepatitis, hypersensitivity reactions (i.e., face edema, thrombocytopenia, leukopenia, vesiculobullous rash, urticaria, and angioedema), kidney failure, syncope, myasthenia, myositis, pancreatitis, photosensitivity reaction, myopathy, and rhabdomyolysis.

Postmarketing Experience

In addition to the events reported above, as with other drugs in this class, the following event has been reported during post-marketing experience with CRESTOR, regardless of causality assessment: very rare cases of jaundice and memory loss.

OVERDOSAGE

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving CRESTOR and should continue on this diet during treatment. CRESTOR can be administered as a single dose at any time of day, with or without food.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb)

The dose range for CRESTOR is 5 to 40 mg once daily. Therapy with CRESTOR should be individualized according to goal of therapy and response. The usual recommended starting dose of CRESTOR is 10 mg once daily. However, initiation of therapy with 5 mg once daily should be considered for patients requiring less aggressive LDL-C reductions, who have predisposing factors for myopathy, and as noted below for special populations such as patients taking cyclosporine, Asian patients, and patients with severe renal insufficiency (see CLINICAL PHARMACOLOGY, Race, and Renal Insufficiency, and Drug Interactions). For patients with marked hypercholesterolemia (LDL-C >190 mg/dL) and aggressive lipid targets, a 20-mg starting dose may be considered. After initiation and/or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

The 40-mg dose of CRESTOR is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of CRESTOR once daily (see WARNINGS, Myopathy/Rhabdomyolysis). When initiating statin therapy or switching from another statin therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's individualized goal of therapy.

Homozygous Familial Hypercholesterolemia

The recommended starting dose of CRESTOR is 20 mg once daily in patients with homozygous FH. The maximum recommended daily dose is 40 mg. CRESTOR should be used in these patients as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. Response to therapy should be estimated from pre-apheresis LDL-C levels.

Dosage in Asian Patients

Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolemia is not adequately controlled at doses of 5, 10, or 20 mg once daily. (See WARNINGS, Myopathy/Rhabdomyolysis, CLINICAL PHARMACOLOGY, Special Populations, Race, and PRECAUTIONS, General).

Dosage in Patients Taking Cyclosporine

In patients taking cyclosporine, therapy should be limited to CRESTOR 5 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions).

Concomitant Lipid-Lowering Therapy

The effect of CRESTOR on LDL-C and total-C may be enhanced when used in combination with a bile acid binding resin. If CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions).

Dosage in Patients With Renal Insufficiency

No modification of dosage is necessary for patients with mild to moderate renal insufficiency. For patients with severe renal impairment ($CL_{cr} < 30$ mL/min/1.73 m²) not on hemodialysis, dosing of CRESTOR should be started at 5 mg once daily and not to exceed 10 mg once daily (see PRECAUTIONS, General, and CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency).

HOW SUPPLIED

CRESTOR® (rosuvastatin calcium) Tablets are supplied as:

5 mg tablets: Yellow, round, biconvex, coated tablets identified as "CRESTOR" and "5" debossed on one side and plain on the other

side of the tablet.

(NDC 0310-0755-90) bottles of 90

10 mg tablets: Pink, round, biconvex, coated tablets identified as "CRESTOR" and "10" debossed on one side and plain on the other side of the tablet.

(NDC 0310-0751-90) bottles of 90

(NDC 0310-0751-39) unit dose packages of 100

20 mg tablets: Pink, round, biconvex, coated tablets identified as "CRESTOR" and "20" debossed on one side and plain on the other side of the tablet.

(NDC 0310-0752-90) bottles of 90

(NDC 0310-0752-39) unit dose packages of 100

40 mg tablets: Pink, oval, biconvex, coated tablets identified as "CRESTOR" debossed on one side and "40" debossed on the other side of the tablet.

(NDC 0310-0754-30) bottles of 30

Storage

Store at controlled room temperature, 20-25°C (68-77°F) [see USP]. Protect from moisture.

Rx only

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Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: IPR Pharmaceuticals, Inc.
Carolina, PR 00984

PCC 630303
30043-02
Rev 01/07 248272



Medical Resources Quality Assurance Survey

Inquiry Number: 602373

Product: CRESTOR

Dear Dr. Roger Citron,

We hope that the data provided to you proved useful. Please take a few minutes to answer the following questions in order to help us determine how well we are meeting expectations. This survey can be:

- Completed online at <http://mrsurvey.astrazeneca-us.com/> with the Inquiry Number listed above.
- Filled out and faxed back to Medical Resources at (800) 640-5886 OR (302) 885-1400.
- Filled out and mailed back to AstraZeneca at:
Medical Resources FOC/CE1-706
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

Adverse Events Reporting

Clinicians are encouraged to report suspected adverse events to AstraZeneca by calling 1-800-236-9933

ADVERSE EVENTS SHOULD NOT BE REPORTED USING THIS FORM

1. Did the response answer your question? ☐ Completely ☐ Partially ☐ Not at all

If you checked "Partially" or "Not at all", please explain:

2. Using the scale below, please rate the following statements concerning the response from AstraZeneca to your inquiry.

	Strongly Agree	Agree	Slightly Agree	Slightly Disagree	Disagree	Strongly Disagree
The information is useful / helpful	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The information is clear and logical / understandable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The information is balanced	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Our response to your inquiry was handled in a reasonable amount of time / timely response	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Overall, I was satisfied with the quality of the information I received.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. In general, how do the responses from AstraZeneca compare to those of other companies?	Superior	Above Average	Average	Below Average	Inferior	Not enough experience to compare
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. What is your profession?	Physician	Pharmacist	Nurse	Physician Assistant	Other	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

6. Please provide any suggestions for changes or improvement in the medical information service provided by AstraZeneca in the space below:

Thank you for taking the time to complete the survey. We hope to use this information to continually improve our services.

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